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Abnormal GABAergic function and face processing in schizophrenia: A pharmacologic-fMRI study

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ABSTRACT

The involvement of the gamma-aminobutyric acid (GABA) system in schizophrenia is suggested by postmortem studies and the common use of GABA receptor-potentiating agents in treatment. In a recent study, we used a benzodiazepine challenge to demonstrate abnormal GABAergic function during processing of negative visual stimuli in schizophrenia. This study extended this investigation by mapping GABAergic mechanisms associated with face processing and social appraisal in schizophrenia using a benzodiazepine challenge. Fourteen stable, medicated schizophrenia/schizoaffective patients (SZ) and 13 healthy controls (HC) underwent functional MRI using the blood oxygenation level-dependent (BOLD) technique while they performed the Socio-emotional Preference Task (SePT) on emotional face stimuli ("Do you like this face?"). Participants received single-blinded intravenous saline and lorazepam (LRZ) in two separate sessions separated by 1–3 weeks. Both SZ and HC recruited medial prefrontal cortex/anterior cingulate during the SePT, relative to gender identification. A significant drug by group interaction was observed in the medial occipital cortex, such that SZ showed increased BOLD signal to LRZ challenge, while HC showed an expected decrease of signal; the interaction did not vary by task. The altered BOLD response to LRZ challenge in SZ was significantly correlated with increased negative affect across multiple measures. The altered response to LRZ challenge suggests that abnormal face processing and negative affect in SZ are associated with altered GABAergic function in the visual cortex, underscoring the role of impaired visual processing in socio-emotional deficits in schizophrenia.

1. Introduction

The role of the gamma-aminobutyric acid (GABA) system in the pathophysiology of schizophrenia has gained increasing attention. Post-mortem studies have provided strong evidence for an altered GABA system in the disorder. One of the most consistent finding has been the reductions of glutamic acid decarboxylase-67 (Akbarian and Huang, 2006; Benes, 2010; Lewis et al., 2012; Nakazawa et al., 2012), a synthetic enzyme for GABA, observed in multiple brain regions associated with critical cognitive functions, including the dorsolateral prefrontal cortex, anterior cingulate cortex (ACC), motor cortex, visual cortex, and hippocampus. Few studies have examined in vivo GABA function in schizophrenia, and while the results have been somewhat mixed (Taylor and Tso, 2014), it remains an important goal to show how GABAergic abnormalities observed in post-mortem studies may be related to the behavioral phenotype of schizophrenia.

GABAergic interneurons are the major machinery of inhibition in the human brain, central to the synchronization and oscillations of neuronal activity that are critical to perception, memory, and cognition (Cobb et al., 1995; Osipova et al., 2006; Wang and Buzsaki, 1996). Clinical observations suggest that altered socio-emotional deficits in schizophrenia may be closely related to GABAergic dysfunction. For example, GABA-manipulating agents such as benzodiazepine and valproate are frequently used to augment antipsychotics and treat negative affect (e.g., anxiety, dysphoria) in schizophrenia (Wassef et al., 1999). Further, these drugs are used to facilitate mood regulation in bipolar disorder (Cousins and Young, 2007), in which glutamic acid decarboxylase-67 abnormalities are also observed in postmortem studies (Guidotti et al., 2000). While increased trait negative affect (Horan et al., 2008) and socio-emotional deficits (Tso et al., 2010) are well-documented phenomena in schizophrenia and have been shown to be important determinants of functional outcome, their association with GABAergic dysfunction has been rarely explored but could advance our understanding of the disease mechanisms of schizophrenia.

In a recent study, we paired a benzodiazepine challenge and blood–oxygen-level dependent (BOLD) fMRI to map GABAergic mechanisms associated with affect processing in schizophrenia (Taylor et al., 2014). We used lorazepam (LRZ), a non-subtype selective benzodiazepine and an allosteric modulator of GABA receptors that potentiates GABA function (Olsen and Tobin, 1990), to probe GABAergic activity during

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passive viewing of emotionally salient images. Schizophrenia patients showed increased BOLD signal in the dorsomedial PFC (dmPFC) and occipital regions in the LRZ condition, instead of decreased BOLD signal found in the healthy controls. This abnormal response was correlated with increased negative affect, providing the first evidence for the involvement of GABAergic dysfunction in affect processing and negative affect in schizophrenia.

In this study, we used the same pharmacologic-fMRI design to investigate the involvement of GABAergic dysfunction in abnormal face processing and its relationship to negative affect in schizophrenia. Face processing is impaired in schizophrenia, although it is unclear whether the impairment is specific to the processing of the socio-emotional aspects of faces or represents a general visual processing deficit (Darke et al., 2013). In previous work, we used a face appraisal task and showed reduced co-modulation between ACC, dmPFC and occipital cortex in schizophrenia, which was correlated with poor social functioning (Taylor et al., 2011). In the current study, we employ this socio-emotional preferential task (SePT), to investigate face processing as a whole, as well as isolate the effect of social appraisal in the dmPFC. We hypothesized that abnormal BOLD response (reduced inhibition or increased activation) to LRZ challenge during face processing would be observed in the dmPFC and occipital cortex in schizophrenia, and these abnormalities would be more pronounced during social relative to non-social appraisal. In addition, we hypothesized that these abnormal fMRI findings would be correlated with increased negative affect in schizophrenia.

2. Methods

2.1. Participants

Seventeen stable, medicated outpatients with DSM-IV schizophrenia or schizoaffective disorder, established by a Structured Clinical Interview for Diagnosis (First et al., 1995), were recruited. Fourteen completed the study and provided usable data. Thirteen healthy control participants were recruited from community advertisements and selected to match the basic demographics (age, sex, and parental education level) of the SZ group. All participants were provided information on the purpose and risks of the study prior to giving written informed consent. The study was conducted in accordance to a protocol approved by the University of Michigan Medical School Institutional Review Board for adherence to ethical standards of research. See Supplementary Methods and Results for more details about the participants.

2.2. Assessments

Clinical symptoms of the SZ participants were assessed by an experienced clinician (S.F.T.) using the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), the Calgary Depression Scale (Addington et al., 1993), and the Scale for the Assessment of Negative Symptoms (Andreasen, 1983). All participants completed the Wide Range Achievement Test, revised, Reading subtest (WRAT3-R) (Jastak and Wilkinson, 1984) for general intellectual achievement and the Brief Assessment of Cognition for Schizophrenia (BACS) for general neurocognition (Keefe et al., 2004).

Prior to each scanning session, participants completed self-report measures of emotional state, including the Perceived Stress Scale (PSS) (Cohen et al., 1983), Spielberger State-Trait Anxiety Inventory (state; STAI) (Spielberger CD et al., 1993), and the Differential Emotions Scale (DES) (Fredrickson et al., 2003). Participant characteristics are summarized in Table 1.

2.3. Task design

The Socio-emotional Preferential Task (SePT) is a simple social judgment task that has been applied in schizophrenia research previously (Taylor et al., 2011). Participants were shown happy, neutral, and fearful faces. Each face was presented for 3 s, and participants were required to press a button to indicate whether the face is male or female (GenderID; "Gender? Male/Female") or whether they like the face or not ("Like? Yes/No"). They were instructed to respond quickly based on their first impression. Faces were displayed in blocks, and each block consisted of four faces of the same valence and task (Like or GenderID), separated by rest periods of 4–8 s where a fixation cross appeared in the center of the screen. Task alternated between blocks, and the order of valence was pseudorandomized. The task consisted of 72 blocks in total over 4 runs, each 368 s of duration (3 valence × 3 blocks × 2 tasks × 4 runs). Prior to the first scanning session, all participants experienced a desensitization run in a mock scanner, in which they viewed stimuli and responded on a button apparatus similar to the actual scanner.

Table 1
Demographic and clinical characteristics of participants.

	SZ (n = 14) Mean ± SD	HC (n = 13) Mean ± SD	t/χ^2	p
Demographics				
Age	43.0 ± 12.6	41.5 ± 12.7	0.30	0.77
Sex (male/female)	9/5	8/5	0.22	0.88
Education, years	15.4 ± 2.7	16.3 ± 2.1	1.00	0.32
Parental education, years	16.5 ± 2.7	14.9 ± 2.8	1.49	0.15
Duration of illness, years	23.8 ± 14.3	–	–	–
CPZeq	398 ± 321	–	–	–
Neurocognition				
WRAT3-R	50.8 ± 7.0	53.5 ± 2.3	1.31	0.20
BACS	−1.5 ± 1.5	−0.1 ± 1.0	−3.00	0.006
Emotion Assessments				
PSS	14.7 ± 5.9	8.9 ± 5.0	2.73	0.011
STAI	33.0 ± 9.1	27.9 ± 4.6	1.81	0.083
DES-positive	2.69 ± 0.53	2.96 ± 0.77	−1.06	0.30
DES-negative	1.07 ± 0.50	0.44 ± 0.29	3.96	0.001
Symptom assessments				
BPRS total	29.5 ± 4.5	–	–	–
BPRS positive	7.5 ± 2.5	–	–	–
BPRS negative	6.0 ± 1.9	–	–	–
CDS	2.1 ± 2.4	–	–	–
SANS global sum	4.9 ± 2.6	–	–	–

Note. CPZeq = antipsychotic dose in chlorpromazine equivalent mg daily. WRAT3-R = Wide Range Achievement Test, revised, Reading subtest. BACS = Brief Assessment of Cognition for Schizophrenia. PSS = Perceived Stress Scale. STAI = Spielberger State-Trait Anxiety Inventory. DES = Differential Emotion Scale. BPRS = Brief Psychiatric Rating Scale. CDS = Calgary Depression Scale. SANS = Scale for the Assessment of Negative Symptoms.

2.4. Scanning sessions

Participants underwent two fMRI scanning sessions in a single-blinded, cross-over design (Fig. 1). All participants had negative urine toxicology screens for drugs of abuse prior to each scanning session. After placement of an intravenous line, they received bolus injections either of lorazepam 0.01 mg/kg, or an equivalent amount of saline solution. Participants were placed in the MRI scanner and the task began approximately 30 min after injection, when blood levels of intravenous LRZ were maximal (Wermeling et al., 2001). Each session consisted of the SePT and another activation task (reported elsewhere).

Prior to the intravenous line placement, before each task, and then again after the scanning session, participants completed 6 visual analogue scales (VAS) assessing their subjective feelings of drowsiness, anxiety, happiness, fear, sadness, and excitement.

2.5. Functional MRI Acquisition

MRI scanning occurred on a GE 3T Signa scanner (LX [8.3] release, General Electric Healthcare, Buckinghamshire, United Kingdom). A T1-weighted image was acquired in the same prescription as the functional